

REMARKS/ARGUMENTS

1. Status of the Claims

Claims 7-20, 24-31, 50-53, and 56-67 are currently pending in the present application. Claim 8 is withdrawn as being directed to non-elected subject matter.

Support for the amendments to claim 25 can be found, for example, in original claim 50 and in paragraph 16 of the specification. Support for the amendments to claim 27 can be found in originally filed claims 27 and 50, for example. Support for the amendments to claim 56 can be found in the specification in paragraphs 90 and 100, for example. The remainder of the claim amendments are made to correct antecedent basis, claim dependency, and typographical or grammatical errors. Support for the instant amendments can be found throughout the specification including the originally filed claims.

2. Priority

The Office acknowledges Applicant's claim for benefit of priority to US Serial No. 09/104,759 which is set forth on page 1 of the specification. Applicants thank the Examiner for pointing out that the status of the '759 patent application was not provided in the specification. Applicants correct this oversight through amendment to the specification above.

3. Claim Rejections Under 35 USC § 112

A. Claim Rejections Under 35 USC § 112, First Paragraph

The Examiner rejected claims 7, 9-20, 24-31, and 50-53 under 35 USC § 112, first paragraph, allegedly as not being enabled for methods of reducing the size of any tumor, elimination of any tumor, or prevention of the formation of any tumor using the claimed methods. The Examiner sets forth that the specification is enabling for methods of reducing the number of lung metastases of a colon carcinoma by intravenous administration of cationic DOTAP:cholesterol liposomes comprising total autologous tumor RNA alone or total autologous tumor RNA and DNA encoding interferon gamma operatively linked to a constitutive promoter.

The test for enablement is whether or not the application as a whole, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation (see MPEP § 2164.01, Revision 5, August 2006).

On page 5, lines 14-18, of the Office Action mailed June 6, 2007 (hereinafter the Office Action), the Examiner asserts that the data provided in the Examples of the specification allegedly do not demonstrate that a CTL response or any other immune response generated was capable of completely eradicating either an established primary tumor located anywhere in the mouse, or any metastases located anywhere in the mouse, or of completely preventing the formation of any solid or liquid tumor or tumor metastases stemming from such tumors. Applicants respectfully submit that in view of the amendments to claims 30 and 31 deleting the elimination and prevention of tumors, the present rejection is moot.

Next, the Examiner asserts that the model system used allegedly corresponds to a local delivery system since the specification teaches that cationic liposome/nucleic acid complexes localize to the lungs (see the bottom of page 5 of the Office Action). The Examiner further alleges that the examples do not demonstrate that the immune response generated would be effective in reducing or preventing the growth of distal [non lung] primary tumors or metastases. This is an unsupported assertion and should be withdrawn. Further, Applicants respectfully disagree because the immune response(s) generated include a systemic, specific and/or non-specific immune response(s). Thus, one skilled in the art would be able to make and use the claimed invention to treat "distal" primary and metastatic tumors because the immune response(s) is/are systemic not localized. Thus, Applicants respectfully submit that, while the Examples demonstrate a high level of localization of the administered nucleic acids in the lungs and demonstrate the treatment of primary and metastatic lung tumors, one skilled in the art would expect, absent evidence to the contrary, that a systemic immune response(s) would target primary and metastatic tumors throughout the body because of the systemic nature of the response(s).

Still further, Applicants claimed invention is not limited to the Examples provided in the specification because compliance with the enablement requirement does not turn on whether an example is disclosed (see, e.g., MPEP 2164.02, Revision 5, August 2006).

Next, on page 6 of the Office Action, the Examiner asserts that allegedly in order for a CTL to kill a target cancer cell, the tumor cell would need to present the same peptide/MHC complex as the stimulating antigen presenting cell. This is an unsupported assertion and should be withdrawn.

The Examiner then asserts that Restifo et al. allegedly teaches mechanisms by which tumors might evade an immune response. Applicants respectfully submit that peptide/MHC complex expression and the mechanisms by which a tumor might evade an immune response are irrelevant to the present invention because the present invention is not dependent upon any mechanism of action, because the Examiner does not provide evidence that tumors actually do evade the immune responses generated by the methods of the present invention, and because the Examples in the specification provide overwhelming evidence that the methods of the present invention actually do treat primary and metastatic tumors.

Next, starting in the middle of page 6 of the Office Action, the Examiner asserts that the use of total RNA derived from multiple allogeneic tumor of the same histological tumor types can be extremely heterogenic. The Examiner supports this allegation of extreme heterogeneity with Chen et al. (1995) PNAS 18(2) 8125-8129 (hereinafter Chen et al.) which allegedly demonstrates that the expression of one gene, gp100, varies in different melanoma tumor with some melanomas allegedly not expressing gp100 at all. Applicants respectfully submit that Chen et al. does not support the allegation of extreme heterogeneity based on variability in expression of one gene in multiple tumor sample.

Still further, the presently claimed invention discloses the use of a plurality of RNA molecules (either coding and non-coding or non-coding alone, depending on the claim). Thus, the present invention is not susceptible to variations in expression of one gene or even a number of genes.

Next, starting at the bottom of page 6, of the Office Action, the Examiner asserts that the complete elimination or prevention of tumors allegedly is not enabled by the

specification as filed. In view of the amendments to claims 30 and 31 deleting the elimination and prevention of tumors, Applicants submit that the present rejection is moot.

B. Claim Rejections Under 35 USC § 112, Second Paragraph

The Examiner rejected claims 7-10 and 66-67 under 35 USC § 112, second paragraph, allegedly as being indefinite.

Applicants note that claim 8 was withdrawn from consideration by the Examiner in the present Office Action.

The Examiner rejected claim 7 allegedly as being an improper Markush group for reciting classes of molecules that allegedly are not cytokines. Specifically, the Examiner asserts that hematopoietic growth factors, immunoglobulin superfamily molecules, and chemokines allegedly are not cytokines. Applicants respectfully submit that the present rejection is obviated in view of the amendments to claim 7.

The Examiner rejected claims 8-10 as being dependent on rejected claim 7. Applicants respectfully submit that claims 8-10 each depend from claim 52, making the present rejection moot.

The Examiner rejected claims 66-67, which each previously depended from claim 50, as allegedly being indefinite because claims 66-67 allegedly relate the RNA of claim 50 to being in the form of a plurality of cDNA sequences and not the RNA itself. Claims 66-67 are amended herein to make the claims dependent from claim 27 and to direct the claims to the further steps of converting said total RNA into a plurality of cDNA sequences amplified from said total RNA, and operatively linking each of said cDNA sequences to a transcription control sequence. In view of the these amendments, Applicants believe that the present rejection is obviated.

4. Claim Rejections Under 35 USC § 102(e)

The Examiner rejected claims 56, 60, and 63 under 35 USC § 102(e) allegedly as being anticipated by US Patent No. 6,670,186 to Nair et al. (hereinafter referred to as Nair et al.).

In view of the amendments to claim 56, hereinabove, Applicant's respectfully submit that the present rejections of claim 56 and dependent claims 60 and 63 are moot because Nair et al. does not teach or suggest a composition comprising a liposome delivery vehicle and non-coding RNA isolated from a mammalian sample.

5. Claim Rejections Under 35 USC § 103(a)

A. The Examiner rejected claims 7, 9-20, 24, 26, 28-30, 50-53, 56-61, and 63-64 under 35 USC § 103(a) allegedly as being unpatentable over US Patent No. 5,589,466 to Felgner et al. (hereinafter Felgner et al.), in view of Nair et al.

The burden is on the Examiner to establish a prima facie case of obviousness and at least the following basic criteria must be met:

- (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
- (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
- (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
- (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. See USPTO Training Guide Published August 31, 2007.

a. Claims 56-61 and 63-64

Claims 56-61 and 63-64, as amended, are directed to compositions comprising a liposome delivery vehicle and non-coding RNA isolated from a mammalian sample. Felgner

does not teach or suggest the claimed composition because, for example, Felgner does not teach or suggest a composition comprising more than one coding RNA molecule. Applicants respectfully submit that Nair et al. does not cure the defects in the teachings of Felgner et al. because, for example, Nair does not teach or suggest a composition comprising non-coding RNA isolated from a mammalian sample. Accordingly, a finding of nonobviousness must necessarily be made because the combination of cited references does not teach each and every element of the presently claimed invention, namely a composition comprising a plurality of non-coding RNA.

b. Claims 7, 9-16, 18-20, and 50-52

Claims 7, 9-16, 18-20, and 50-52, as amended, are directed to a method to elicit a systemic, non-specific immune response in a mammal, comprising administering to the mammal a therapeutic composition by a route of administration selected from the group consisting of intravenous and intraperitoneal administration, said therapeutic composition comprising: a liposome delivery vehicle; and non-coding RNA isolated from a mammalian sample.

Felgner does not teach or suggest the claimed method because, for example, Felgner does not teach or suggest the use of a composition comprising more than one specific type of coding RNA molecule. Applicants respectfully submit that Nair et al. does not cure the defects in the teachings of Felgner et al. because, for example, Nair does not teach or suggest the use of a composition comprising non-coding RNA isolated from a mammalian sample. Accordingly, a finding of nonobviousness must necessarily be made because the combination of cited references does not teach each and every element of the presently claimed invention.

Furthermore, prior to the disclosure of the present invention, it was not known that administration of a liposome delivery vehicle and non-coding nucleic acids to a mammal resulted in the elicitation of a systemic, non-specific immune response in the mammal. Accordingly, one skilled in the art would not have seen, at the time the application was filed, that this solution to the problem of how to elicit a systemic, non-specific immune response would have a reasonable expectation of success. Still further, the cited art teaches away from the

presently claimed invention in that the cited art teaches to use coding nucleic acid sequences to elicit an immune response.

c. Claims 17, 24, 29-30, and 53

Claims 17, 24, 29-30, and 53, as amended, are directed to a method to elicit a tumor antigen-specific immune response and a systemic, non-specific immune response in a mammal that has cancer, comprising administering to the mammal a therapeutic composition by a route of administration selected from the group consisting of intravenous and intraperitoneal administration, said therapeutic composition comprising: a liposome delivery vehicle; and total RNA isolated from a tumor sample, said RNA encoding tumor antigens, wherein said cancer is selected from the group consisting of a primary lung cancer and a pulmonary metastatic cancer.

Each of the present claims, as amended, depend from claim 27 which is now written in independent form and was not rejected for obviousness in the instant Office Action. Accordingly, Applicants respectfully submit that the present rejection is moot in view of the amendments to claim 27 and to claims 17, 24, 29-30, and 53 which now depend from claim 27.

d. Claims 26 and 28

Claims 26 and 28, as amended, are directed to a method to elicit a tumor antigen-specific immune response and a systemic, non-specific immune response in a mammal that has cancer, comprising administering to the mammal a therapeutic composition by a route of administration selected from the group consisting of intravenous and intraperitoneal administration, said therapeutic composition comprising: a liposome delivery vehicle; and total RNA isolated from a tumor sample, said RNA encoding tumor antigens, wherein said total RNA is isolated from a plurality of allogeneic tumor samples of the same histological tumor type.

Claims 26 and 28 are amended to depend from claim 25, which is now written in independent form, and was not rejected for obviousness in the instant Office Action. Accordingly, Applicants respectfully submit that the present rejection is moot in view of the amendments to claim 25 and to claims 26 and 28 which now depend from claim 25.

B. The Examiner rejected claim 62 under 35 USC § 103(a) allegedly as being unpatentable over Felgner et al. in view of Nair et al and US Patent No. 5,830,878 to Gorman et al. (hereinafter referred to as Gorman et al.). Applicants respectfully submit that the present rejection is moot in view of the amendments to claim 56 for the reasons stated above, since claim 62 depends from claim 56.

6. Claim 65 Is Not Rejected

Applicants respectfully submit that claim 65 was not rejected in the Office Action and request acknowledgement of the allowability of claim 65.

All subject matter canceled by way of amendment in the present application, including in the present Response, is done so without prejudice or disclaimer as Applicants reserve the right to pursue any canceled subject matter in a later filed application.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Michael J. McCarthy", is written over the typed name.

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